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The Medical treatment of peptic ulcer with special emphasis on the injection method

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THE MEDICAL TREATMENT OF PEPTIC ULCER

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INJECTION METHOD

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INTRODUCTION

Cancer, pulmonary actinomycosis, leukemia and a host of other such diseases entail in the making of such a diagnosis, dealing the patient a very hard blow. The prognosis, though reserved, is with few exceptions extremely bad, and the physician knows the patient will die within a varying period of time because of that disease in spite of the strenuous attempts to combat it.

Pernicious anemia, diabetes and others have ceased to be the dread diseases they formerly were, and the mortality per se has become the exception rather than the rule. With a relative few exceptions, and these are complications of the disease rather than the disease itself, peptic ulcer entails no fear as to mortality.

Sympathy may be sincerely extended to one whose house and belongings are burning to the ground, and whose wife and children consequently become homeless. Yet, no one can have nor feel the same emotions, the fear, the same mental misery suffered by the one involved.

I do not believe anyone except the patient having an ulcer can emotionally experience the mental and physical misery which such a condition brings about.

The history of an ulcer patient may be somewhat as follows:

In the beginning, perhaps a supreme unconsciousness of doctors, disease, ill health, hospitals, waiting rooms, and drug store shelves loaded with magic properties.

Then--a vague unrest, an uncomfortable feeling in the pit of

the stomabh, a feeling of fullness, and perhaps some slight tenderness. Attributable of course, to that heavy dinner of fowl, or the brocali, or perhaps to the "night before".

Forgotten for the moment. The attributed cause abstained from too. Yet the "feeling" persists and what is worse becomes with each succeeding day more and more pronounced. That supremely unconscious consciousness is finally penetrated, and the knowledge that there is something the trouble, comes to the fore.

The vague feeling no longer present but in its place a tight constricting feeling. The uncomfortableness disposed by a more worthy opponent....pain. Pain which strikes to the marrow of the individual. A leech-like sharpness which causes the days to be endless....the nights an eternity of hell.

Consequently, he goes to a physician and after extensive tests and examinations is diagnosed as "ulcer". Then begins a series of events which tax his already over-taxed mind. Periods of well-being alternate with periods of his "trouble". After a period of months he has been on a number of therapeutic changes, but none seem to work any better than the one before. He has been advised to have an operation, but the idea failed to "take" because one of his friends had an operation for ulcer and now there is another ulcer which is even worse than the first one.

Finally, he tries another physician. He is strongly advised to have an operation, but since he refuses is put on some "new stuff". That helps for a while but sooner or later he has the same old trouble.

The months have turned into several years. He has been to three physicians. During this time he has not had a square meal. He does not smoke, drink, and his favorite--coffee was taken from him long ago. His work has suffered,and his wife and he do not seem to get along as well. He is afraid to go out for an evening of bridge, or a dance, or the theatre because he is never quite sure whether he is going to get through an evening without being nauseated or vomiting or having that almost unbearable pain. Anyhow, he has to take that "stuff" every two hours, and if his friends have lunch later in the evening he feels out of place. He wonders if he will every get complete relief?

Meanwhile, the "ulcer" sits merrily back on its haunches and chortles with glee.

At best, a pathetic picture, and one all too frequently, correct.

The purpose of this paper, therefore, will be an attempt to determine what factor or factors must be attacked to change this picture to a happier one, and to attempt to evaluate the various therapeutic methods to determine what agent or agents will most effectively do this.

DEFINITION

"A circumscribed area of the mucous membrane or wall of the stomach or adjacent duodenum, through malnutrition or necrosis, loses its normal resistance to the peptic action of the gastric juice and becomes digested. The resulting defect is an ulcer."[1]

Furthermore,[2] a peptic ulcer is limited to the stomach, the bulb of the duodenum, the jejunum which has been anastomosed, as in a gastro-jejunostomy, with the stomach, and in rare cases the lower end of the esophagus in close contact with the stomach. In other words, to those anatomic areas subjected to the action of gastric juice containing pepsin and free hydrochloric acid.

HISTORY

No isolated anatomic description of the lesion found in ulcer of the stomach appeared until the sixteenth century although observations regarding the existence of round ulcers date back to the time of Galen.

The first clear description of the morbid anatomy and symptoms of gastric ulcer was published by Baille[3] in 1793. Abercrombie[4] of Edinburgh in 1882 published more complete observations of both gastric and duodenal ulcer with recommendations as to treatment.

Cruveilhier, by presenting his classical observations, formed the foundation of the present day knowledge. It was he, who made

clear the distinction between simple benign ulcer of the stomach and cancer.

Other distinguished names in the history of the development of knowledge of this disease are those of Rokitansky and Virchow who first employed the term "corrosive ulcer of the stomach", and recognised the part played by the digestive juices in its pathogenesis.

The introduction of the modern term "peptic" or "digestive" ulcer was made by Quincke.

ETIOLOGY

Before any disease can be really successfully treated its causal agent must be determined, otherwise, there results as many or more methods of treatment as there are theories of etiology.

If this has not been accomplished, the next most suitable means is a thorough study of the possible agencies at play in an attempt to obtain a rational basis for treatment.

Bevan[5], states that the essential causes of peptic ulcer are now well known and are practically those first recognized by Rokitansky and Cruveilhier. Peptic ulcer is due to the action of a number of factors. Pettenkofer very admirably represented these by means of an algebraic formula which he sets forth as an explanation of the cause of disease. He believes most diseases to be due to a combination of factors and repre-

sented by the formula: X plus Y plus Z equals a given disease which might be a carbuncle, pneumonia, or an ulcer of the stomach.

When this formula is applied to an ulcer of the stomach, X represents the essential and most important factor, which in peptic ulcer is the gastric juice containing pepsin and free hydrochloric acid. Y is some injury or disease of the stomach wall which so impairs the vitality of the tissue that it can be digested by the gastric juice, as disease of the blood vessels, inflammation or injury. Z is composed of a great number of factors that lower the general resistance of the patient or increase his susceptibility; these might be anemia from any cause, syphilis or tuberculosis, a hereditary susceptibility or nervous tendency with its resulting effect on the sympathetic or pneumogastric nerve supply.

Much information has been gained by autopsy regarding incidence and sites of peptic ulcer formation.

The incidence of peptic ulcer, either gastric or duodenal, occured in 5% of all autopsied deaths from various causes.[6] Robertson and Hargos[7] of the Mayo Clinic found 19% of all autopsies revealing ulcer and of this 19%, 65% were duodenal and 35% gastric. Approximately then, in the neighborhood of 12% of all autopsies show active or healed evidences of ulcer.

The distribution of the ulcers of the stomach according to Sippy[6] are as follows:

"25% in the lesser curvature

30% in the posterior wall

12% in the pylorus

9% in the anterior wall

6.5% in the cardiac portion

3.5% in the greater curvature

3% in the fundus

1% in the cardiac orifice"

75% to 80% of all ulcers of the stomach proper occur in a relatively small area on the posterior surface of the lesser curvature near the pyloric orifice; as Sippy said, "An area not larger than a silver dollar".

This was substantiated by Einhorn[8]. Brinton's 205 ulcer cases revealed 42% on the posterior surface and 26.8% on the lesser curvature. Fenwick's 1015 cases of gastric ulcer showed 76% situated in the region of the pylorus and on the posterior surface. Collins in a study of 262 cases, found in 242 cases, the ulcer in the first part of the duodenum. Bolton corroborates this by noting that ulcers of the duodenum occur with remarkable frequency and constancy, in the anterior wall of the organ and in 95% of these cases in the first part of the duodenum.

There must be, then, some explanation for this restriction of peptic ulcer. It is known that for an ulcer to develop anywhere in the body regardless of location, there must be an area of malnutrition with a break in the continuity of the surface membrane

followed by necrosis and subsequent ulcer formation. The same general law applies to peptic ulcer.

Fischle,[6] of Germany states that after thirty years of continuous study of patients with gastric ulcer, he has never detected a case where achylia gastrica was present, and, whenever tests revealed the entire absence of hydrochloric acid and pepsin, the erroneous diagnosis of ulcer was later confirmed.

Einhorn,[8] by means of anatomic reasons explains this restriction of lesions to the area making up the lesser curvature, the pylorus, and the first part of the duodenum.

The pyloric wall is firm, strong, and well developed and is composed of thick muscle bundles, while the fundus has much thinner walls. The submucosa is also firmer, bulkier, and better developed in the pyloric region than in other portions of the stomach. It is adherent to the mucosa in this region but is more lax in the fundus, where it enables the mucosa to become more convoluted when the muscular coat contracts.

Also, the mucosa in the pyloric region is closely attached, smooth, and thick, while in the fundus it is thin. The pylorus is sparsely supplied with folds and the convolutions are numerous, freely movable, and without definite arrangement. The longitudinal mucosal folds in the lesser curvature are stretched and under tension, while in the fundus they become redundant and convoluted.

Furthermore, the pylorus is provided with pyloric glands only, while the fundus possesses oxyntic cells, which secrete acid. The central cells, which form the pepsin and other digestive ferments, also are in the fundus. The acid forming cells extend for approximately 60.7% of the distance from the cardia to the pylorus, along the lesser curvature, and 83% of the distance between the orifices along the greater curvature.

Moreover, the fundus receives its blood supply from the main source through three different branches, while the pylorus is supplied from the same source through two branches only. The fundus is supplied from the main source and one primary branch, hence the amount of blood per volume is greater there than in the pylorus, which is supplied only by primary and secondary branches, the distance they traverse being longer, and the amount of blood per volume much less. The arteries in the pylorus are practically terminal vessels, sparsely distributed and tortuous. They anastomose infrequently and they are subject to powerful constrictions by numerous interlacings, frequently contracting muscle bundles. The arteries in the fundus are not terminal, are less tortuous, anastomose more freely, and on account of the scarcity of interlacing muscle bundles, are less subject to constrictions.

The muscles of the pylorus are bulky and heavy, for it bears the burden of the food, mixes it with the acid gastric juice, and breaks it down by muscular action. The fundus serves merely as a reservoir to contain the food and does not take an important part in

the mechanical activity of the stomach, hence its muscles are much thinner than those of the pylorus. The muscles of the first part of the duodenum, as well, are much thicker than in any other part, and the sphincteric rings and mucosal folds, which are lacking elsewhere, are located in this region. Glands known as Brunner's glands are more numerous in this first part of the duodenum. Moreover, the first part of the duodenum is under greater tension than the remainder of it, because of the force exerted by the food which is expelled from the pylorus. The mucosa in this region, which is constantly imbedded in the alkaline secretion, is frequently damaged by the mixed acid foods which are expelled from the stomach.

The acidity of the stomach has been treated with much respect as being of marked importance in peptic ulcer.

According to Bensley and Harvey,[9] hydrochloric acid first exists in the free state in the foveola. There is no acid in the gastric glands. Moreover, in the canaliculi of the parietal cells there exists an alkaline substance. Therefore, only the antecedents of the acid are formed within the gland. Actual hydrochloric acid is not produced, therefore, by the parietal cells, but instead they secrete an alkaline forerunner of it which is changed to acid outside the cells.

Boldyreff[10] states that the acidity of the freshly secreted gastric juice is constant being 0.5% Hcl. He believes this acidity to be rapidly lowered to a level which oscillates between 0.15 to

0.2% Hcl and that any acid foreign to the stomach when introduced undergoes the same process. His explanation of this partial neutralization is that a reflex of alkaline juices from the duodenum occurs--the pancreatic juice being the most important. This mechanism which maintains the optimum level of acidity, 0.5 0.2% Hcl he calls the "self-regulatory mechanism of the acidity of the stomach contents".

Morton,[11] believing acidity to be a definite cause of ulcer, has produced experimentally in dogs, lesions which tend to substantiate his belief. He first produced experimental ulcers in normal dogs and then in dogs in which the alkaline duodenal secretions had been side-tracked so that it was impossible to get into the stomach.

By isolating the duodenum from the stomach, cutting the jejunum and putting it into the terminal ileum and at the same time anastomosing the distal cut end to the pylorus, he produced what he terms "surgical duodenal drainage". Gastric contents were thus propelled directly against the jejunal wall, while the alkaline duodenal contents emptied direct into the ileum close to the cecum. In dogs in which he had not performed this operation ulcers were experimentally produced. These ulcers produced in dogs in which regurgitation of the duodenal secretions took place healed spontaneously. The ulcers produced in dogs on which he had performed his surgical procedure side-tracking duodenal secretions and pre-

venting regurgitation did not heal but became chronic just like those in the human. In 100% of his cases, a chronic jejunal ulcer was formed where the stream of acid stomach contents struck against the intestinal wall.

These facts would tend to prove the importance of acid in ulcer production and furthermore, the importance of alkaline duodenal regurgitation in neutralizing the excess acidity. Moreover, an impairment of this regurgitation is most certainly a factor in permitting a persistant high gastric acidity and favors malignancy by continued irritation.

What then influenzes this alkaline regurgitation?

Cannon has insisted that the pylorus is caused to open by the acid on the stomach side and when the acid has passed through to the duodenal side closure of the pylorus occurs.

Devine,[12] as emphatically insists that the sympathetic nervous system imposes a certain retention tone or posture on the gastric muscle. Any alteration in this posture, governed by the labile sympathetics, deranges the natural alkaline duodenal protective regurgitation controlling the acidity and probably initiates a set of circumstances which may eventually lead to ulcer.

Thus, instead of the acid controlling pyloric activity, the pyloric activity controls the acid. Hence, a spasm or stricture of the pylorus would hinder alkaline regurgitation. Devine has

called the sympathetics which control this gastric musculature, "labile", and Gaskell[13] believes that these sympathetics take the stress and strain of modern life and are undoubtedly subject to psychic influences and that consequently abnormal development, irritability, or disease of the sympathetic system can alter the postural tone of the gastric and duodenal muscles and thus the emptying time of the stomach with faulty regurgitation.

According to Wiggers[14] when either the splanchnics or the vagi are cut there is an immediate slowing of gastric motor activity with a decrease in tone. Recovery, however, takes place so that the emptying time of the stomach is prolonged and this is the only permanent effect.

When the vagus nerve is stimulated there is an increase in contractility and tone of both fundus and body, but in the pyloric region including the sphincter, this increase occurs only when tone is low and a decrease or inhibition occurs only when tone is high.

When the splanchnic's are stimulated there arises inhibitory effects usually, but excitatory results may be obtained if the tone is low.

Crile[15] believes that there is enough clinical and experimental evidence to indicate that hyperacidity and hypermotility are controlled by the nervous system and the thyroid and

suprarenal glands, which exhibit a reciprocal relation. He states that a reciprocal, independent group of organs, forming a working system, apparently is best modified by removing a part of each. Accordingly, he has performed in five cases of intractable or recurrent ulcers of the stomach, a partial thyroidectomy and suprarenalectomy. In every case there resulted a decrease in gastric and intestinal motility and disappearance of the symptoms of ulcer.

Bolton and Rosenow have performed interesting experiments in attempting to determine the etiology of this disease.

Rosenow[16] revived the bacterial theory of ulcer etiology advanced many years ago by Boetcher, Letulle, Dieulafoy and others, and has, by means of tissue culture shown the importance and significance of bacterial action originating from local or disseminated foci of chronic infection. Intravenous injections of streptococci obtained from lesions of the mouth and throat and which culturally, have undergone mutation to some degree, have produced both acute and chronic gastric ulcer. He has recovered organisms from these ulcers which morphologically and culturally appear similar to those with which he produced the experimental ulcer. He has also demonstrated the existence of an interrelationship between infections of the appendix, gall-bladder, pancreas and peptic ulcer where the streptococcus is concerned. However, as the definitive causative agent or factor of gastric

ulcer and particularly as to its being the only cause this bacterial proof of Rosenow cannot be entirely accepted for the reason that other organisms used by investigators as well as a variety of non-bacterial agents have also yielded ulcers which do not appear to be essentially different from those of Rosenow's. Moreover, he has failed to demonstrate that the organisms recovered from these ulcer areas have not been secondary invaders.

Bolton has performed an extensive experimental study previous to Rosenow. Be means of non-bacterial tissue injections he has produced quite uniformly all grades of ulcer in susceptible animals. He has taken sterile emulsions of the gastric mucosa, appendix, gall-bladder, or liver and injected this emulsion intravenously or intraperitoneally producing a toxic serum in the injected animals. He has shown that this toxic serum in 10-14 days has such selective affinity that its introduction into the circulation of other animals produces ulceration and necrosis in the organs from which the original cell emulsions were made.

He obtained the most marked reactions with gastric cell emulsion which caused acute hemorrhagic ulcers; these ulcers later becoming chronic. The toxic quality of this serum was destroyed by saturating with gastric cells. By this process Bolton produced a serum which was immune and which he termed "gastro-toxin". He believed this immune serum indicated that a wide spread destruction of body cells took place due to a variety of diseases of a consti-

tutional nature, and from this destruction and disintegration poisons were elaborated which were specific with respect to the tissue from which they were derived. Great waste occurs in the stomach as a result of constant functional demand and this cellular waste satisfies the essentials of a protein poison. Thus, this poison is capable of producing local cell changes in the gastric mucosa and this change furnishes the anlage for a subsequent ulcer. Moreover, when this initial local injury has taken place, the autodigestion of the mucosa by gastric juice or its ability to harbor bacteria are possible and not until then.

Before the subject of etiology is finished some slight mention should be made as regard the role of nicotine in peptic ulcer. Cole[17] states that nicotine and alkaloid, which have been proved to be the chief ingredients of tobacco, has a peculiar affinity for the autonomic nervous system, first stimulating and then depressing the ganglia. His 100 patients under observation and study during a period of three years were divided into two equal groups, the first showing a functional gastric disturbance, the second, organic gastric disturbance. Cole's findings were that the first group exhibited distinct variations in secretory and motor findings as a result of tobacco and the resulting hypersecretion and hyperacidity he attributed to the tobacco. A few in this group designated as having gastritis showed a hypo-acidity. His second group, with duodenal ulcer, showed an increase

in gastric secretion and acidity and in increased peristalsis. In a few members of this group the emptying time was delayed.

TREATMENT

To the internist, the surgeon, the general practitioner, and the medical student the term "Ulcer" immediately brings to mind the word "Sippy". Conversely, "Sippy" means "Ulcer".

Yet Sippy did not inaugurate his widely publicized treatment until the early years of the Nineteen Hundreds. Peptic ulcer was recognized as a disease entity many years previous--in the days of Virchow, Cruveilhier, Rokitansky. What then was the treatment of the disease previous to the time Sippy plucked the "Corrosion theory" Von Leube had pronounced inadequate forty years previous, and on the basis of this theory scattered to the four winds his Sippy Regimen?

We find that Williams[18] gives one of the earliest accounts of treatment of ulcer in 1874. He cites a case where the symptoms were principally hematemesis, pain in the left hypochrondrium and a certain amount of nausea. The case was diagnosed peptic ulcer and treated by applying a blister to the left hypochrondrium and the administration of mistura gentiana alkalina t.i.d. The hematemesis was treated by giving 20mm. of Oil of Turpentine. Gallic Acid in X gr. dosage $\bar{q}$ 4 hours and opium for the pain as well as creosote, belladonna, and $AgNO_3$ were also given. Nutritive

enemata were given for a ten day period and William's believed that we possessed a valuable and effective stomach in the rectum which might not afford us the pleasures of digestion, but certainly spares us the pains of that process.

Redmond[19] in 1882 observed that iodoform had a marked healing action in external ulcer. Believing it might be equally efficacious in peptic ulcer, iodoform gr. III in a pill was given t.i.d. in association with nutritive enemata and a blister to the epigastrium. The vomiting stopped in two days and the patient discharged in a month's time.

Davis[20] believed that a case presenting itself for medical treatment required the following care. Rest--of the body in general and the stomach in particular. To rest the stomach he advised feeding by rectum, or a limited diet by mouth. He believed the feeding by rectum to be the best, but cautioned that great care must be observed. The frequency of feeding he believed best accomplished by starting with a 4 oz. quantity and administering this amount every six hours. In the morning before the nutritive enema was given the bowels were flushed out with hot saline. Davis used peptonized milk, eggs, and "Mellins Food".

At about this same period many other men were advocating their preference in the treatment of this disease.

Osler preferred to feed by mouth with a regular diet of

beef solution, peptonized milk, and milk gruel four times a day.

Tyron gave 2 oz. of peptonized milk every two hours.

Da Costa administered an exclusive diet of ice-cream.

Lockwood used a combination method. For three days rectal feedings alone were given. From the third to the seventh day, 6 oz. of equal parts of milk and lime water were given every two hours in association with the rectal feedings. A change to the regular diet was gradually accomplished. As medicaments, Bismuth and silver nitrate headed the list and opium was given for pain.

Lichty[21] states that the indications for treatment of gastric ulcer are to overcome the pain and discomfort and to meet or prevent dangerous hemorrhages or perforations. He believes that a course of treatment which nearly meets all of these was outlined by Von Leube and Ziemessen years ago. Von Leube placed a high value on physical and functional rest. The highest possible state of nutrition was accomplished by withholding food for 5-10 days and then feeding by bowel for 10 days gradually adding soft non-irritating foods most likely to combine with Hcl to the diet and administering by mouth. Lichty found bismuth subcarbonate in large doses very efficient. He used Ag No_3 as he believed it depressed the activity of the gastric cells and also coated with mucus the gastric membrane. Belladonna or atropine were used as they were believed to exhibit an effect by inhibition on the

gastric secretions. Alkalies were advocated where there was marked hyperacidity.

Craig[22] reviewed the subject of ulcer in 1910. At that time he stated that hyperacidity was recognized as the cause, and this could be neutralized by the administering of alkalies, but at best this procedure was only temporary and might prove harmful. The Lenhartz treatment was advocated. Moreover, the administering of a ferruginous preparation such as dried sulfate of iron to take up the excess Hcl was set forth. He remarked that rest, milk diet, relief of constipation by bismuth and alkali mixture and also iron formed the basis which most physicians of his country depended upon at this time. He strongly advocated the use of the Lenhartz treatment.

LENHARTZ TREATMENT

The failure of Von Leube[23-24] to allow sufficient caloric intake to present the undernutrition so common to this type of treatment moved Lenhartz to attempt to provide more than the 350-1200 calories Von Leube allowed in the first 14 days of his treatment. The fear of starting another hemorrhage had been the principal reason physicians had for the previous 25 years refrained from administering food. Lenhartz advocated an immediate feeding even though there had been a hemorrhage the previous day. He thus showed that food could be given immediately. He also encouraged constipation even to having the patients refrain from having a

bowel movement for several days in an attempt to cut the intestinal activity to a minimum. His strenuous advocacy of the binding power of egg albumin and other proteins gave a tremendous impetus to protein therapy. For medication 30 grs. Bismuth subnitrate t.i.d. for the first 10 days was used.

SIPPY REGIMEN

Sippy[1] believes the principles involved in treating ulcer are centered around certain vital fundamental questions, namely:

1. The cause or causes of peptic ulcer.
2. The factors retarding or preventing its healing.
3. The determination of the most efficacious methods to promote granulation tissue which is essential to healing and ultimate cicatrization.

He believes that the digestive action of the gastric juice to be due to the pepsin acting upon albuminous substances previously permeated by Hcl. These conclusions result from the knowledge that pepsin is to all intent and purpose inert in alkaline and neutral media while in combined acid media it acts but slightly and combined acids are incapable of acting upon albumins so that pepsin may work. However, a free acid such as Hcl freely permeates and allows pepsin to act as a solvent.

If, as Sippy states, an ulcer of the stomach or duodenum would heal as rapidly as an ulcer located elsewhere if its granulating

surfaces were not subjected to the digestive action of the gastric juice, then any mode of treatment which would efficiently and persistently nullify by neutralization or otherwise this gastric juice, should, regardless of the etiologic factor involved, promote healing where all other means fail which are not based on this principle.

This principle is involved in Sippy's treatment and the shielding of the ulcer from the corrosive action of the gastric juice is what Sippy attempts to accomplish by neutralization which is efficiently managed by frequent feedings and the use of alkalies in carefully regulated but adequate amounts. This neutralization is not only maintained from 7 A.M. until 10:30 P.M. when food and secretions are present in the stomach, but determinations are made and steps taken to overcome any night secretions. If there are secretions present at night, and in case of duodenal or pyloric ulcer associated with stagnation, this is practically always the case, aspirations of the stomach and removal of these secretions are meticulously carried out. After three to four days this excessive nightly secretion disappears if accurate control is maintained and the gastric glands are allowed to become less irritable.

In detail Sippy's treatment follows.

A. "Where the ulcer is of the non-obstructive type".

1. Rest:--In bed for three weeks.

2. Diet

First three days--3 oz. of a mixture of milk and

cream, equal parts, every hour from 7 A. M. to 7 P.M.

After three days--soft egg may be added to the 10 A.M. feeding. 3 oz. cooked cereal to the 3 P.M. feeding of M.C.

After seven days--3 oz. M.C. every hour, 7 A.M. to 7 P.M. Soft egg 10A.M. noon and 2 P.M. feeding. 3oz. cooked cereal 11 A.M., 1 and 3 P.M.

After fourth week--the patient leaves the hospital and goes on a routine to be followed for one year.

3. Alkaline Medication:-

Powder No. 1

Heavy Calcined Magnesia Gr. X

Sodium Bicarbonate Gr. X

Powder No. 2

Bismuth Subcarbonate Gr. X

Sodium Bicarbonate Gr. XX or XXX

First three weeks powder No. 1 given with M-C from 7 A.M. to 7 P.M. If diarrhea results Powder No. 2 is substituted for No. 1. On the half hour between feedings from 7:30 A.M. to 7:30 P.M. powder No. 2 is given. Then every half hour to 9:30. Olive Oil or powder is given at 2:00 A.M.

4. Aspiration of Stomach

Two afternoons and three evenings each week until the physician is satisfied gastric secretions are completely neutralized. If there is excessive secretions the powders are continued up to 11:00 P.M. and a M-C mixture may be given at 2:30 A.M.

5. Routine to be followed for one year.

Three small meals daily consisting of a soft diet, the total bulk for each meal not to exceed 10-15 oz. After breakfast a powder every half hour for three doses.

10:00 A.M. M-C Mixture 3 oz.

10:00 A.M. Powder

11:00 A.M. M-C Mixture 3 oz.

Noon--Lunch

After lunch a powder every half hour for three doses.

3:00, 4:00, and 5:00 P.M. 3 oz. M-C Mixture.

3:30, 4:30, and 5:30 P.M. a powder.

6:00 P.M. Night meal which should be small.

After night meal a powder every half hour for four doses.

Now and then patient allowed to take regular meal.

Patient to make arrangements to have available M-C mixture at all times. All powders should be discontinued at the end of the 10th week, and at the end

of every six weeks thereafter.

B. "Where the ulcer is of the obstructive type"

This type of case is one in which Sippy maintained he could offer an extremely high degree of success. Believing that most cases of this type represented the result of an inflammatory edema with marked round cell infiltration rather than an organic cicatrix he asserted that this inflammation would quickly subside if the gastric secretions were rigidly controlled. Absolute control of acidity and absolute bed rest are the fundamentals of his treatment. More care is necessary regarding aspiration as neutralization by alkalies, according to Sippy, may not completely control. The treatment is continued until progress is satisfactory or until no doubt is present that surgery must be sought.

THE ALVAREZ METHOD

Alvarez[25] regards the treatment of ulcer inadequate. He has been impressed by the fact that patients report symptomatic relief by the taking of food every two hours, and regards "frequent feedings" not only practical and successful in a therapeutic manner, but helpful also in a diagnostic manner especially where X-Ray fails to reveal a deformed cap or definite evidences of an ulcer. No other lesion of the digestive tract responds so characteristically.

Rest in bed, frequent feedings, alkalization and eradication of focal infection are the points recommended by Alvarex who believes frequent feedings the most important and demands his patients have three good meals a day chosen from a "Smooth Diet" and the taking of a 6 oz. misture of eggs, milk cream, or thin gruel at 10:00 A.M. 2, 4, 8 and 10:00 P.M. and during the night, if awake. This is continued for 6 months or a year. Alvarez is skeptical of a permanent cure for ulcer under any type of treatment.

Medication in the form of alkalies such as bismuth, magnesia, or soda he believes to be unimportant and states, "I have not prescribed it more than five or six times in the last thirteen years".

THE SMITHIES TREATMENT

Smithies[16-26] based his treatment on a physiologic rest regimen which has for its principles.

1. "The recognition that ulcer is not a primary gastric ailment; treating it as such without bearing in mind its systemic or constitutional origin offers little hope of permanent improvement."
2. "Recognition of the ulcer at hand."
3. "The opinion that gastric chemistry plays a comparatively insignificant role in ulcer production and in delay of ulcer healing. Ulcer dyspepsia is largely due to abnormal gastric spasm, peristalsis and intragastric tension."

4. "Recognition of the need of physiologic rest and the natural tendency to heal should not be interferred with."

His method of treatment follows:

Rest in bed-- one to three weeks--securing in this manner both mental and physical rest.

Physiologic rest to the stomach by withholding food and medicines and performing no lavage. This is done for three to seven days. Healing is thus promoted by limiting local irritation and peristalic movements.

Nutritive enemas during the fasting period. When feeding by mouth is begun the food is mainly carbohydrates; warm, in liquid form, and of small quantities.

Regarding acidity, he believes this to be controlled by the fasting phase of his treatment as little secretion is to be found after a period of 48 hours.

Moreover, he doubts if any medicine has a direct healing affect upon peptic ulcer.

NEWER METHODS OF TREATMENT

In the past ten---fifteen years numerous methods have gained prominence in the literature in the treatment of peptic ulcer. Perhaps physicians were finding it too strenuous a piece of work to maintain the Sippy Regimen at the peak at which it climbed following its initial presentation after which it supplanted to a large degree

those therapeutic measures then in vogue. Perhaps the many doctors of philosophy were turning their attentions toward the experimental basis of ulcer. Perhaps, the popularity of the Sippy Regimen was in itself its undoing, as each man using it had his own peculiar and particular "modification".

At any rate a crying need must have been felt for some therapeutic means which would give better results, since at best, those on hand were not too successful and the rigors of a Sippy Regimen were enough to frighten everyone but the physician who suffered not at all in ordering so nonchalantly "Sippy".

The need made known, in a span of a few years, there spun out on the markets of therapy a host of agents till we find at present[27] various strains of organisms and vaccines, pepsin, sodium benzoate, vaccineurin, novaprotein, hemoprotein, sodium citrate, parathyroid extract, insulin, emetine hydrochloride, and histidine monohydrochloride, being used parenterally, and metaphen, mucin, aluminum hydroxide, powdered okra, as non-parenteral new methods with river sand or silicon dioxide the latest.

NON-PARENTERAL METHODS

Metaphen

Trippe[28] has used metaphen orally with a great deal of success. Although a mercurial compound he has used it routinely on his ulcer cases and found no cases of toxicity, and reports that some patients

have continued the administration of this drug at a dosage of 16 cc daily for months without reporting bad effects. Trippe has found with close laboratory check and assistance that metaphen taken orally is not excreted in the urine, but is recovered in the stools. He reports the use of metaphen, "In practically all cases relief from pain in three days in spite of the fact most patients had suffered for years".

Technique of Administering

4 cc doses t.i.d.

4 doses First week

3 doses Second week

2 doses Third week

1 dose Fourth week

Then every other day for a week. Then cessation of treatment.

He reports 82 cases, 26 of which were gastric, 56 duodenal. Confirmatory X-Ray diagnosis in 27 of the 82 was made. Following treatment, with metaphen, complete disappearance of the ulcer as proved by X-Ray.

Aluminum Hydroxide

Attempting to obtain some agent which would more efficiently handle the gastric juice, Woldman and Rowland,[29] have used a 7% colloidal suspension of $AlOH_3$ which they found would adsorb 20-25 times its volume of N/10 Hcl. They found that a fresh washed flocculent precipitate of the hydroxide made from $AlCl_3$ was very

efficacious, but that the dry powders or tablets broke down to the oxide or other inert substance which had little affect as an antacid. An increase in the power of adsorption was found when a washed precipitate underwent colloidal milling.

Technique

A number 12 small Levin tube was passed thru the nostril. A specimen of gastric juice was drawn off for analysis and also to show the tube was in the stomach. A 200cc 7% colloidal $AlOH_3$ was added to 600cc of distilled water and stirred until well mixed. By means of an air tight system the $AlOH_3$ was allowed to drip from the Levin tube so that in 24 hours, 800cc were emptied from the bottle. By this method a constant and equal amount of the $AlOH_3$ is present in the stomach at all times, and the marked fluctuation so commonly present when alkalies are administered is not a problem.

They found the results of this means of therapy very efficacious. Prompt relief of pain, especially night pain was almost without exception. A constant achlorhydria was proved by A.M. and P.M. samples. X-Ray confirmed the diagnosis before treatment in all cases. The startling point brought out is the rapidity with which pain disappeared, and the disappearance of the ulcer radiographically in 7-14 days. One particular case is cited in which the patient had persistant pain, had been in bed for four weeks on a Sippy Regimen, and surgery was deemed unavoidable. As a last resort $AlOH_3$ was tried. All pain disappeared in a week and an X-Ray film at the end

of seven days failed to show the niche which had prviously been seen.

Adams, Einsel, and Myers[30] have used a colloidal cream of $AlOH_3$ in which 1 cc neutralizes 20 cc of 10/N Hcl in a period of four hours.

They conclude on a large number of cases that:

1. It does not impair gastric secretions.

2. There is a decrease in the total amount of acid which is more marked in hyperacidity.

3. As far as the acid-base balance is concerned, no change occurs in the serum chlorides, total base, or carbon dioxide contents. They believe there is a small tendency for the total chlorides and carbon dioxide to fall away from alkalinity.

4. The use of $AlOH_3$ over a period of several months is not followed by a disturbance in the acid-base balance.

5. There is a marked, immediate effect on pain and other symptoms when $AlOH_3$ is used.

6. That $AlOH_3$ is by far the most efficient and satisfactory antacid to be employed to date.

Mucin

Jones[31] has used mucin since 1931 on 30 cases and believes it to have a definite place in therapeutics especially in certain intractable cases.

Fogelson[32] corroborates this and believes mucin to be an ideal therapeutic agent in combatting gastric juice in peptic ulcer. He believes it neutralizes or combines with the acid without stimulating or depressing gastric secretions. Two ounces of mucin in the stomach of a dog was more than sufficient to combine with the acid secreted in response to an injection of 1 mg. of Histamine. Fogelson found that the use of mucin gave complete relief of symptoms for varying periods of from 2-5 months in twelve patients with classical histories and positive X-Rays. He fed his patients an ounce of gastric mucin t.i.d. with meals in addition to about 30 grs. in tablet form hourly throughout the day.

Hydrated Magnesium Trisilicate

Mutch,[33] has attempted to discover an efficient antacid. In the use of hydrated magnesium trisilicate, he believes he has not only discovered this, but an additional aid directly, as concerns the ulcer. As an antacid he has found 1 gm. neutralizes 310 cc. of N/20 Hcl. Magnesium chloride is produced by the process as well as an insoluble residual of hydrated silica.

It is brought out that in turning to a gelatinous mass due to the acid, and since its power as an antacid is sustained for hours even in excess acid, it furnishes a basis for local antacid therapy, and in the ulcer bed progressively neutralizes the acid diffusing through, even though pepsin digestion is taking part in other parts of the stomach.

It is the opinion of Mutch, that the adsorbing power of this drug is sustained and not exhausted in a few hours or even a few days, and consequently cannot be saturated with foodstuffs from the gastric contents.

Moreover, it is maintained that it has a strong antiseptic power which is available for the protection of the ulcer base from destructive digestion.

Furthermore, not only the parent substance....magnesium trisilicate....but the end product of its chemical breakdown.... hydrated silica....act with effectiveness in promoting healing. As the adsorbtive power of the parent substance is utilized, hydrated silica is liberated in a form which possesses marked adsorbtive affinity for pepsin, food poison, and other substances.

The preparation can be given in large doses without disturbing the general motility or producing constipation or diarrhea, and no matter how large a quantity is given the gastric secretion are not reduced materially below the neutral point--PH 7. It has the added advantage of not being absorped.

Dosage

A dosage ranging between 7-28 grains is given midway between each feeding so that not more than 5-21 grains is received by a patient at a time. In 15 cases as cited, only in one did the dosage exceed 16 grains.

One to four teaspoons of an emulsion of paraffin in a watery

dispersion of colloidal koalin is administered about one-half hour before meals in order to eliminate attrition at the ulcer site and impedance at the pyloric and duodenal-jejunal flexure. The dosage is determined by bowel action.

PARENTERAL METHODS

Insulin

Danzer[34] believes the cause of ulcer to be due to the characteristic circulation of the gastric mucosa. The patchy hyperemia in the mucosa he regards as the cause of mucosal necrosis. To correct the impaired circulation in the mucosa, and to stimulate the ulcer to heal he used insulin by mouth as he believes it has an effect on the anabolic activity of the cells as well as a capillary effect. Distilled water is also used by Danzer as he believes it has, when injected intravenously, a biocellular effect. A concentrated vitamin effect is also produced by the use of vitamin B and ultra-violet light.

Some difficulty was experienced in administering insulin by mouth as it became absorped too rapidly to effect a local gastric reaction until it was mixed with bismuth subcarbonate.

Technique

Fifteen drops of insulin U 20 are mixed with one-half teaspoon of bismuth subcarbonate. This is stirred and allowed to stand for

one-half hour when it is again stirred. It is then swallowed slowly thirty minutes before the meal t.i.d.

Obviously, this is therapeutic "gun-shot" and distilled water, bismuth, and vitamins have each been used singly and with marked "success" by various writers. Consequently, there is no foundation from a scientific standpoint that insulin exerts any effect per se on the ulcer.

Pepsin

Pepsin injections have also been claimed to be of value in ulcer treatment. Here again, however, the previous objection holds true.

Glaessner[35] has used pepsin in treating ulcer patients, but has placed them on bismuth medication, alkali powders, and used olive oil five times a day as well as maintaining a rigid diet.

Hemoprotein (Brooks)

Proteins have been used fairly extensively in treatment. The principles are the same for all. The non-specific proteins usually used are typhoid vaccine, containing killed typhoid bacilli; vaccineurin, a bacterial autolysate of staphlococcus aureus and bacillus prodigiosus; novaprotein, a crystalline vegetable protein; aolan, defatted sterile milk; proleolac; and hemoprotein.

Levin,[36] has used a number of these protein preparations and believes hemoprotein (Brooks) to be the best. It is an ox-blood

fibrin which supposedly acts as a general antigen and tissue stimulant as well as a "resistance builder". It possesses low toxicity and does not produce reactions or protein shock.

Levin makes an initial injection, without a preliminary desensitizing dose, starting with 0.1 cc and increasing, sometimes daily, by 0.1 cc for about seven days and then every other day until a maximum of 2.0 cc is reached. The patient is under observation for a period of about six months, and on a soft diet. The treatment is ambulatory.

Sodium Chloride and Sodium Citrate

Butman[37] believes that sodium chloride aids the circulatory processes, and reduces blood volume. He further believes that sodium citrate has anticoagulatory properties, lessens the tendency toward clotting, aids in the direct circulation of the tissues, stimulates cell activities and mentions the fact that both these substances have been used with much success in thrombo-angitis obliterans.

In preparing these substances they use a combination of the two, buffered to the correct hydrogen ion concentration, by means of a buffered salt. Triple distilled water is used under pressure and the solution transferred to aseptic 20 cc glass ampules.

It has been used on 22 cases, 20 of which were duodenal, and 2 gastric. They report very "favorable" results and report their colleagues have obtained the same "favorable" results in over 100

cases. They believe it worthy of merit because,

1. They believe a circulatory impairment or deficiency is probably the basis of ulcer.

2. They believe it promotes healing by improving the acid-base balance of the blood and improving the circulation, both direct and collateral, to the ulcer bearing area.

3. It makes the tissue more resistant to digestion by the gastric secretions.

4. It brings about a general systemic increase in the circulation and increases general "resistance".

Two or three injections are given per week until twenty-four injections are given. Then an injection every two to four weeks for a period of twelve months.

There is no basis for the "opinions" as stated. They may be true but no proof has been advanced. To date it is "just another ulcer treatment".

Emetine Hydrochloride

For a number of years,[38] Holler, Pribram, Mueller and Peterson attempted to control gastric function and check hypermotility of the stomach. They were able to produce hypo-peristalsis, lessen the amount of free hydrochloric acid, and induce a hyperemia and increased vascularity about the ulcer areas as well as augment the production of gastric enzymes and total enzymes by the use of

of proteins. Unfortunately, they were able to control these functions for only 1-1½ hours. When they reinforced the protein with lipoids and lipins a more sustained action resulted. Finally, in emetine they found a synergist which controlled gastric function for a period of 96-120 hours. Moreover, the emetine had a marked culmulative affect so that following 5-6 injections a more normal function was maintained.

Emetine hydrochloride is on the market under the name "Synodol". One ampule is given every third or fourth day for a series of 10 injections.[39] It is advised that the injection be made slowly about 3-4 hours after the noon meal, as otherwise vomiting may result, with the patient in the prone position as some dizziness has been reported by several authors.[38,39,40] Nothing in the form of a reaction has been reported except one or two cases[39] where some muscular soreness was present following several injections which lasted for several days.

In a series of 127 cases Pitkin[38] has found all cases to be made free from pain, more comfortable, with healing of the ulcer as shown by radiographs, in an unstated number of instances. He believes bland foods essential in this treatment and heartily endorses its use.

Cunha[39], in a comprehensive number of cases has studied carefully the use of this drug. He has 29 cases which he cites in which treatment has been completed for a period of at least

a year. Each patient was checked radiographically previous to treatment and every three months thereafter. In another series of 22 cases which had been receiving treatment during the past 12 months, he has checked radiographically every three months. In this second group varying periods of less than one year has elapsed since completion of treatment.

In both of these series of cases smoking, drinking tea, coffee, and indulging in alcoholic beverages was prohibited. He is of the opinion that a smooth bland diet is necessary for the first ten days and thereafter, chicken, lamb-chops, cereals, and fruit may be added.

His results for these two series of cases has been excellant as in all but two cases complete relief was accomplished and pain which he has found to be the most constant and most severe symptom has been completely and promptly relieved. Furthermore, he cites four patients who have resumed their excessive use of alcohol without return of symptoms.

Olpp[40] has used this agent in over 400 cases and obtained complete relief in every case in periods varying from three days to a week. He has had 30 recurrences, each with a history of alcoholic excess.

Upham,[41] in reviewing various types of treatment says, "Synodol, containing emetine, is mentioned only to condemn it".

Olpp,[40] agrees with various writers as to its toxicity, but believes it to be safe in therapeutic doses, and fails to perceive any reason why its use should be discontinued any more than strychnine or arsenic.

Watson[42] has used emetine in the treatment not only of peptic ulcer, but external ulcers, pulmonary tuberculosis, and amebiasis and reports no harmful affects.

Histidine Monohydrochloride

The basis for the use of histidine dates back to the time of Exalto[27] who was the first to produce peptic ulcers in dogs identical to those observed in man. However, his experiments were few and his work unrecognized for years until in 1923, Mann and Williamson[43] reported their results.

They devised experiments by which they diverted the secretions which neutralize the gastric juice as it leaves the stomach, to another portion of the intestine removed from the point of emergence of the acid. They found in a high percentage of cases that under such conditions typical subacute or chronic peptic ulcers, quite comparable pathologically to those found in man, developed in the intestinal mucosa just adjacent to the gastric mucosa.

Then in 1932, Mann and Bollman,[44] reported a large series of experiments and their results. The pylorus was sectioned and the distal end inverted. The jejunum was transected a few centimeters

distal to the ligament of Treitz and the distal end anastomosed to the jejunum and the proximal end to the ileum. Consequently, the gastric contents were expelled from the stomach into the jejunum without becoming mixed with the secretions poured into the duodenum which are drained into the ileum. Furthermore, the possible protective mechanism of the duodenal mucosa was eliminated by substitution of the jejunal mucosa. By means of this procedure they produced, in a series of 100 investigations, peptic ulcer in about 95% of cases.

These results were later confirmed[27] by Ivy and Farley, Morton, Raudin, and Weiss.

Weiss and Aron[27] in reporting their results held the opinion that the absence of duodenal juice affected especially the digestion of proteins and believed that the proteins arrived in the jejunum as gross polypeptids after the albuminoid molecule had been liberated by the gastric juice, but failed to be broken down further to the assimible components, the amino acids, because the jejunal secretion was deprived of the pancreatic trypsinogen which is indispensable to this chemical process. Histidine is thus lacking, and they believe it to be one of the amino acids which cannot be synthesized by the body....the others being cystine, lysine, and tryptophan.

Consequently, with this as a basis, Weiss and Aron repeated their experiments using a daily subcutaneous injection of histidine and tryptophan mixture. Two untreated controls died, but four receiving this daily injection remained happy and sprightly although

they showed the effects of denutrition. On two of the treated dogs after five weeks, on one after six weeks, and on one after ten weeks, an autopsy revealed the mucus membrane to be normal and no ulcers were found.

They repeated the experiment after daily injections of lysine, tryptophan and histidine. They found Cystine too difficult to inject. Injections of tryptophan or lysine did not change the evolution of the ulcer. Injections of tryptophan and histidine combined or histidine alone did.

Devoto[45] agrees that muciparous cells may need amino acids for secreting mucus, but does not see how a deficit of amino acid can occur especially tryptophan and histidine. He believes proteins either homologous or extraneous to the system when administered intravenously or hypodermically have a beneficial effect due to an improvement in the vacular supply around the ulcer and brings about a dimunition of gastric tonus and contractions. He believes tryptophan and histidine belongs to components of protein and may act, therefore, in the same manner.

Subsequent to this experimental work the introduction and use of histidine followed. Reports first appearing in the literature were made in languages other than English.

Hessel[46] reported 22 cases, 18 of which had a duodenal ulcer, 4 a gastric. In 16 cases following histidine treatment no radiologic demonstration could be made and in the remaining, diminution in size

was recorded in every instance. Most of these patients made a gain in weight, and in several a decrease in the gastric curve was noticed.

Bogendoerfer[47] with thirty cases to report claimed that all patients showed improvement.

Bulmer[48] made the first report in the English language on fifty-four cases shown as follows:

TOTAL CASES 54

Treatment completed 52

Under treatment 2

Group A

Symptom free with normal radiogram

Duodenal 8

Gastric 22

Duration of Symptoms- 2 weeks to 8 years

Average 2 years

Group B

Symptom free with abnormal radiograms

Duodenal 3

Gastric 7

Duration of Symptoms - 2 weeks to 5 years

Average 2 years

Group C

Failures

Duodenal 6

Gastric 6

Duration of Symptoms--4 weeks to 9 years

Average 4½ years

Follow-Up

Total cases 36

A.	Still symptom free	15	Relapsed 3	Untraced	1
B.	Still symptom free	7	Relapsed 0	Untraced	1
C.	Still failures	7	Improved 1	Untraced	1

Too Recent

Total cases 16

A.	Symptom free	Normal radiograms	11
B.	Symptom free	Abnormal radiograms	1
C.	Failures		4

Immediate Results of Histidine Treatment

1. 58% symptomatic cures with disappearance of radiographical abnormality.

2. 19% symptomatic cures with persistence of some radiographical abnormality.

3. 23% failures.

Follow-Up

1. Three patients relapsed and one apparent failure improved.

2. Cases of gastric ulcer seem more amendable than

than duodenal ulcer and those with shorter histories react more favorably than those with longer histories.

In the American literature the first ot make any reports were Volini and Mc Laughlin[49] who reported 21 cases. These patients were ambulatory, allowed tea and coffee, nuts, candy, tobacco, and placed on a diet of excessive roughage. They found that histidine produced a rapid clinical improvement. Pain, vomiting, hypersecretion, and retention quickly improved or disappeared. Moreover, the patients appetite and weight increased.

Smith[50] reported 12 cases in which confirmatory X-ray diagnosis had been made. Five of these patients were treated as ambulant cases, seven in the wards. All were given an ordinary diet and no other medication was administered. In all twelve of these cases symptomatic and radiographic cures were obtained.

Rafsky[51] reported 26 cases, 24 of which were duodenal. He found that in one-quarter of these cases there was a marked diminution of acidity almost to the point of anacidity. The pain was alleviated in a comparatively short time, and the patients showed a definite gain in weight. 19% of these cases had remained symptom free for an unstated period of time. Those not responding had penetrating ulcers with definite niche deformity.

Wilhelmy and Hashinger[52] state that in 26 ulcer cases proved radiographically, the disappearance of pain took place about five

days after the first injection. They state, "the patients expressed a feeling of buoyancy and well being at the conclusion of the treatment". In three cases they were unable to obtain relief with histidine, but cite the fact that these three cases had found it impossible to obtain relief from any previous type of medical routine or management.

Love[53] reports 18 cases as follows:

2 cases--doubtful relief. Ulcer still present.

4 cases--considerable relief. Ulcer still present.

3 cases--almost or entirely symptomatic. Ulcer smaller but detectable.

9 cases--symptom free. No evidence of ulcer by X-ray.

He believes histidine compares favorably with orthodox medical treatment, but stated that more investigation was needed.

Lovell,[54] in reporting 14 cases in which X-rays were taken before and after, gives his results as follows.

11 cases--symptom free. Ulcer healed as shown by X-ray.

1 case --symptom relieved. Ulcer still present.

2 cases --no relief from symptoms. Ulcer still present.

Wingfield[55] states that in no case has any undesirable reaction occurred from his use of histidine hypodermically and believes its use a marked aid in the treatment of ulcer.

Tidy,[56] on the negligible basis of five cases, concludes that

histidine protects the mucus membrane or prevents the action of some destructive factor other than Hcl. He found in the five cases reported that the immediate results were very successful.

Gardiner,[57] on 12 consecutive cases, using 5 cc of a 4% solution gave 25 injections and reports that on a follow-up of these cases 9 were symptom free, and 3 had recurrences. He believes that this form of treatment is simpler, no irksome diets must be followed, and it is more economical. From these cases he believes at least a temporary loss of symptoms is brought about, but does not believe histidine has a direct healing effect and will not bring about a lasting cure.

Weigand[58] using 24 injections each on 12 cases, although he does not consider this number to be a fair criteria, believes its use should be further studied, and that its use should be further studied, and that its use should be considered in recurrences after surgery. The prompt symptomatic relief occurring after its use, he believes, should lead to a greater reliance on the X-ray in follow-up studies and not too great a trust in clinical observations.

Jones[59] in discussing this subject does not believe that any new treatment is properly evaluated in less than two years. He has used histidine and found that it improved cases in a manner similar to diets, alkalies, intravenous emetine, and insulin. He doubts

however, the efficiency of one course of treatment no matter how potent in promoting healing and remarks that if histidine is lacking in the body and it is necessary to inject it to heal an ulcer, why is it not necessary to maintain a continuous supply to maintain a proper balance?

Martin[60] in comparing histidine with a diet alkali regimen reports 81 cases. Forty-one of these cases were placed on histidine after positive X-ray's had been obtained. He found the immediate response to be fairly uniform.

His results on Histidine follows:

1. Thirty patients relieved of symptoms at or before conclusion of treatment.

2. Fourteen of the asymptomatic group showed X-ray evidences of healed ulcer.

3. Twelve craters were still present.

4. Eleven showed no improvement symptomatically or radiographically.

5. Twenty-six relapses occurred.

6. Observations extended over a period of six months to one year.

On diet--Alkali Regimen.

Forty patients studied for a perior of time comparable to that of histidine.

1. Thirty patients symptom free at end of this time.

2. Twenty-four relapses.

3. Observations extending over period of ten months to one year.

He concludes from this study that:

1. A better response is obtained with diet alkali than with histidine.

2. Histidine appears only to alter the "rhythm" of the ulcer.

3. No constant effect on Hcl secretion was obtained with Histidine.

4. Histidine appears to be harmless in the quantity used.

5. The clinical improvement with histidine appears to be symptomatic and transient.

Dowden[61] cites a recurrence following a gastroenterostomy in which histidine was used for a month daily followed by emetine every third day for seven injections. No effects were obtained either symptomatic or radiographically. A resection of the stomach including the ulcer bearing area followed with subsequent complete relief. He believes, therefore, that when proper dietary methods and proper alkaline treatment fails to bring relief that all other methods will fail and eventually surgery will be required.

Flood and Mullins,[62] attempting to study the use of histidine, made this study using controls. From 18 cases with positive X-ray's,

12 were given 5 cc normal saline intragluteally, and 6 were given 5 cc of 4% larostidin or histidine. Their results follow:

1. One daily injection of saline for about three weeks resulted in relief of pain in 8 of the 12.

2. Histidine daily resulted in relief in 4 of the 6.

Consequently, they believe on the basis of this study that psychotheray is the factor rather than the solution or drug used, and that this is emphasized by the relief of pain following saline injections. Moreover, they believe that the evaluation of any substance to be tested should be controlled by inert substances.

Sandweiss[27] in 1935 made a very comprehensive study of histidine and attempted to compare it with the standard diet-alkali management of an ulcer.

He believes the proper evaluation of any new therapeutic measure from a clinical standpoint should answer certain basic fundamental questions, namely:

1. "Does the new method under consideration produce a higher percentage of remissions in unselected groups of ulcer patients than does the diet-alkali regimen?"

2. "What percentage of patients not responding to the standard diet alkali regimen become symptom free when the new method is instituted?"

3. "Does the new treatment permit patients to tolerate a maintenance diet dooner than the standard treatment?"

4. "Does the new method prolong the symptom free interval or prevent recurrence?"

5. "Does the new method have any effect on gastric acidity?"

6. "What effect does the new method have on the ulcer deformity as seen by X-ray?"

7. "Does the new method of treatment produce reactions of untoward effect?"

In attempting to answer these questions Sandweiss has studied sixty-nine consecutive patients with the following history.

1. "83.6% had ulcers five years or longer.

2. 90% of patients treated with histidine had ulcers five years or longer.

3. 83.6% or 56 patients had several previous ambulatory treatments.

4. 58.2% or 39 patients had had one or more previous rigid bed-rest Sippy managements.

5. 22.4% or 15 patients had previous appendectomies.

6. 19.4% or 13 patients had had a previous ulcer hemorrhage.

7. 9% or 6 patients had had a gastroenterostomy.

8. 4.5% or 3 patients had had perforations.

9. 1 patient had had a gastroenterostomy with a later resection and finally a partial gastrectomy.

10. 1 patient had had a gastroenterostomy which was "undone"."

Consequently, twenty-three patients were placed on histidine.

Forty-six patients were placed on a diet alkali regimen. Those not responding to one form of treatment were placed on the other form so that seven patients on histidine were placed on diet alkalies and seventeen patients not responding to diet alkalies were placed on histidine. The following were thus treated.

1. 53 patients treated by diet alkali.
2. 40 patients treated by histidine.

Of the histidine series--

1. 40 patients treated.
2. 869 injections.
3. 32 patients received 24 injections.
4. 4 patients received from 12-21 injections.
5. 4 patients received from 6-11 injections.
6. 14 patients treated in the hospital.
7. 26 patients treated ambulatory.

Results of the histidine series.

1. 55% remissions.
2. 20% moderately improved.

Of the Diet Alkali series.

1. 11 patients treated in the hospital.
2. 42 patients treated ambulatory.

Results of the Diet Alkali series.

1. 51% remissions
2. 20% moderately improved.

After Diet Alkali management had failed 17 patients were placed on histidine.

1. 52.9% became symptom free.

2. 17.6% became moderately improved.

After histidine treatment had failed 9 patients were placed on Diet-Alkali.

1. 42.8% became symptom free.

2. 28.6% became moderately improved.

By changing from one unsuccessful treatment to another form of therapy in an attempt to "tire out the ulcer".

1. 73.5% became symptom free.

2. 13.4% became moderately improved.

Recurrences

1. 85% of patients treated with histidine developed recurrences within six months.

2. 31% on diet alkali management developed recurrences within six months.

Acidity--patients treated with histidine.

1. One-third of patients showed slight increase in acid curve.

2. One-third showed a slight decrease.

3. One-third showed no change.

Radiological studies of patients treated with histidine

1. Of 24 patients checked by X-ray or operation not one showed disappearance of the ulcer.

Reactions.

1. 16 of the 40 (40%) histidine treated patients developed mild reactions.

2. Author does not believe a reaction means patient will become symptom free nor that a reaction is necessary for success.

The author does not believe that histidine should be used routinely, but its use should be confined to those cases in which diet and alkali fails to give the desired results--an "extra artillery" as he describes it. When used in these cases, he believes about 50% will become symptom free and 20% moderately improved.

Furthermore, the author is convinced that 24 injections are unnecessary to produce remissions or to prolong the symptom free period. "If 5 or 6 injections do not cause complete disappearance of all ulcer discomfort, the hope of producing remissions or prolonging the symptom free interval by further treatment is negligible."

Sandweiss[63] in a very recent article has made a further comparative study of diet alkali and parenteral treatment in which he has placed emphasis on the number of attachs observed, rather than the number of patients.

A series of two hundred ninety -one patients were observed during 1019 ulcer attacks. From this basis of study, Sandweiss has made certain findings which may be listed as follows:

1. Private patients were found to be more satisfactory in their response than clinic patients.

2. Patients having acute ulcers were found to show a higher percentage of symptom free intervals in comparison with patients having chronic ulcers.

3. 90% of the private practice patients became symptom free when treated with dieat alkalies. The recurrences of the ulcer after six months was least pronounced in all patients treated with diet alkali as compared to patients treated by parenteral methods which included larostidin, synodol, vaccines, and distilled water, being approximately 35% as compared with 70%. Regardless of treatment, however, recurrences occurred after varying periods in practically all patients.

4. Patients not responding to diet alkali and placed on parenteral treatment--larostidin, synodol, vaccines, in about 60% of cases became symptom free. In 22 patients distilled water was used with comparable results.

5. The author does not believe that histidine or emetine, or dead bacteria are the cause of the remissions as distilled water produces the same results.

6. The short duration of remission and the high and immediate percentage of recurrence after parenteral therapy, he attributes to

the dietetic management....general non-restricted diets.

7. Of 155 patients treated medically or surgically, after a five year or longer observation, only five were still symptom free. Consequently, the author places little trust in any form of therapy as far as lasting effects are concerned.

8. He does not believe parenteral treatment should be given routinely in ulcer, but should be confined to those not responding to diet alkali and if used should be in association with, and not in place of, a bland dietary regimen.

9. There is, according to Sandweiss, no specific parenteral ulcer product at the present time. Only a slight difference exist between the results of the various products mentioned, and if one form is unsuccessful another may give better results.

CONCLUSIONS

There are numerous theories as to the etiology of ulcer. Each has its followers, and each appears to have some basis for its promulgation. Yet no single theory has proved to be the sole etiologic agent. Consequently, at the present time we are forced to accept the dualist cause of ulcer which may not be the same in every case.

Consequently, until the cause of ulcer is found or its causal agents more thoroughly understood, the successful treatment of ulcer cannot be obtained, and the profession must manage to do the best they can with the weapons at hand.

The single most important factor, in the retardation of healing at least, appears to be the gastric juice. Consequently, any method of treatment which adequately controls this factor should give the best results.

It would appear, if this were true, that the strict management set forth by Sippy should most efficiently accomplish this.

I am convinced that if these premises set forth above hold true that the strict and only the strict management should be put into practice. I do not believe that modifications of the Sippy Regimen will accomplish the results hoped for.

The various newer methods should not be dismissed lightly, and the profession should cease to be narrow minded in thinking about these various agents of therapy. Sufficient time has not elapsed to

determine accurately the efficiency of these new methods. However, I do not believe that mucin, metaphen and their like will have any lasting place in therapeutics for the general run of ulcer patients.

I do think that $AlOH_3$ and especially Magnesium Trisilicate are worthy of further investigation. If they are as effective in controlling gastric acidity as they are claimed, a most effective weapon will be in the hands of the profession in combating this single most important factor and the rigorous regimen of Sippy will be discarded.

Concerning the injection method of therapy, I believe that the benefits derived, are the same as those obtained from the administration hypodermically of any protein. Moreover, I do not believe that it is the histidine in larostidin which gives the results, but because the amino acid is a basic protein compound.

Moreover, the psychic effect obtained cannot be over-looked in some instances as distilled water....a supposedly inert substance.... gives comparable results.

Since, for best results, only the strict Sippy should be used, and since in the majority of instances such a procedure is highly impractical from an economic standpoint, it would seem that modifications of the regimen must be carried out. I do not think this alone should be relied upon, but should be re-inforced by other methods--namely, injection of some substance perferably, histidine, emetine hydrochloride or other protein compounds.

Injection treatment should not be carried out routinely, but only as an adjunct to standard treatment since the percentage of recurrences is unduly high.

In conclusion, I would like to say that I am not in favor of the Sippy regimen as I do not believe the results warrent its rigorous maintenance. Yet, at present, there is no denying that nothing has taken its place and since this is the case, we are forced to accept it. I am impressed with the antacids employed, namely, $AlOH_3$ and particularly Magnesium Trisilicate. In spite of the fact that only a very few cases have been treated by these means, I feel that there is a well founded basis for an extensive clinical test. This is not true of the many other agents set forth and which have given such marked "success".

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